Chemical Correlations of α-Santonin with (+)-Junenol and Acolamone

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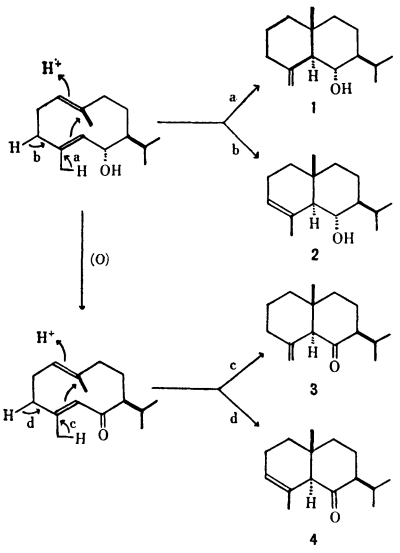
The chemical transformation of the acetoxy ketone (**5**), which has previously been obtained from α-santonin, to (+)-junenol (**1**) and acolamone (**3**) has been carried out. In addition, isojunenol (**2**) was also derived from **5** *via* the trisubstituted olefin (**9**) which was obtained as the main product from the α- and β-oriented mesylates (**8** and **11**) on treatment with NaI in HMPA.

From a biogenetic point of view, the selinane-type sesquiterpenes [(+)-junenol (**1**),[1] isojunenol (**2**), acolamone (**3**) and isoacolamone (**4**)[2]] should be produced from such a common intermediate as a ten-membered ring compound with an (*E,E*)-1,5-cyclodecadiene system, as is shown in Scheme 1.[2] Of these four selinane-type compounds, isojunenol (**3**) has not yet been found. In the present paper, we describe the chemical transformation of the known acetoxy ketone (**5**)[3] to these selinane-type sesquiterpenes. The results indicate that they have the same absolute configuration as α-santonin.



Scheme 1.

The acetoxy ketone (**5**) was reduced with $NaBH_4$ in EtOH (room temp, overnight) to give a mixture of α- and β-hydroxy compounds in a 98% yield (**6**, 27%; **7**, 71%). The further treatment of the latter with mesyl chloride-pyridine afforded the corresponding mesylate (**8**) in a 98% yield; it was directly converted into a trisubstituted olefin (**9**) and a disubstituted olefin (**10**), in 65 and 22% yields respectively, on treatment with NaI in HMPA (80 °C, 3 h) under a nitrogen atmosphere [**9**, δ 1.65 (3H, br.s) and 5.32 (1H, br.s) ppm; **10**, δ 1.01 (3H, d, J=6.5 Hz) and 5.45 (2H, complex) ppm]. Furthermore, the mesylate (**11**) obtainable from **6** in a 92% yield was also treated with NaI in HMPA to give **9** and **10** in 54 and 20% yields respectively. The trisubstituted olefin (**9**) which was obtained from **5** in a 56% overall yield was used for the next experiment, as will be described below.

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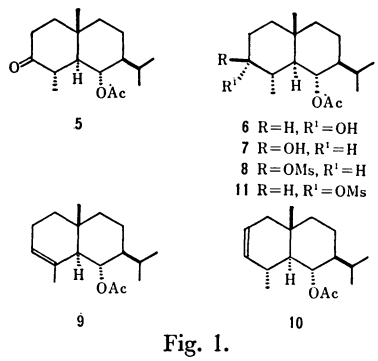

Fig. 1.

The epoxidation of **9** with *m*-chloroperbenzoic acid (under reflux, 3 h), followed by $LiAlH_4$ reduction, afforded a dihydroxy compound (**12**) *via* an epoxide (**13**); the compound was further converted into an acetate (**14**) in an 87.4% overall yield on acetylation with Ac_2O–pyridine (100 °C, overnight).

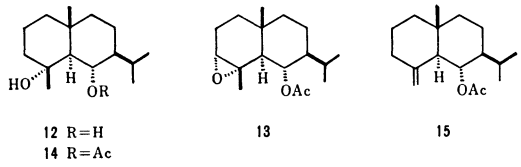

Fig. 2.

Finally, compound **14** was converted into (+)-junenol (**1**) and then into acolamone (**3**) as follows. When treated with $POCl_3$–pyridine at 0 °C for 1 h and then at room temperature overnight, **14** was converted into the corresponding dehydration product, (**15**) [δ 4.45 (1H, br.s) and 4.73 (1H, br.s)ppm], in a 94% yield; it was then reduced with $LiAlH_4$ in ether (under reflux, 2 h) to give, in a quantitative yield, (+)-junenol (**1**); mp 61—61.5 °C (lit, mp 60 °C); $[\alpha]_D^{23}$ +53.1 ° (c=1.07 MeOH) (lit, +52°).[1] The further oxidation of **1** with pyridinium chlorochromate in CH_2Cl_2 (room temp, 30 h) afforded acolamone (**3**) as a colorless, viscous liquid in a 78% yield.

The chemical correlation between acolamone (**3**) and isoacolamone (**4**) has already been established.[2] Surprisingly, though, isojunenol (**2**) has not been isolated from any source. However, on treatment with $LiAlH_4$ in ether (under reflux, 2 h), the olefin (**9**) was readily converted, in a quantitative yield, into isojunenol (**2**); mp 77—78.5 °C; $C_{15}H_{26}O$; ν_{max} 3380 br. cm^{-1}; δ 1.91 (3H, br.s), 3.51 (1H, br.t, J=10.0 Hz), and 5.36 (1H, br.s) ppm.

Experimental

All the mps are uncorrected. IR spectra were recorded on a Hitachi-215 spectrophotometer. NMR spectra were obtained on a Nihondenshi JNM-PS 100 (100 MHz) NMR spectrometer, using $CDCl_3$ as the solvent, unless otherwise stated. The chemical shifts are given in ppm relative to the internal TMS, and only prominent signals are cited (d, doublet; m, multiplet; q, quartet; s, singlet; t, triplet). Mass spectra were obtained on a Hitachi RMU-6D mass spectrometer operating at an ionization energy of 70 eV. Preparative TLC were carried out on Kieselgel PF_{254} (E. Merck, A. G., Germany), unless otherwise stated.

Reduction of the Acetoxy Ketone (5) with $NaBH_4$. Into a solution of **5** (140 mg) in EtOH (4 ml) we stirred $NaBH_4$ (20 mg). The resulting solution was further stirred at room temperature overnight, and then diluted with ether (30 ml) and washed with water. After having been dried over anhydrous Na_2SO_4, the ethereal solution was concentrated under reduced pressure to give a crystalline solid (140 mg), which was subsequently separated by preparative TLC using 5% Et_2O–$CHCl_3$ to give an α-hydroxy acetate, **6** (38 mg), and a β-hydroxy acetate, **7** (100 mg).

6 as colorless prisms: mp 115—116 °C (from hexane); ν_{max} (KBr) 3510, 1720, and 1270 cm^{-1}; δ 0.81 (3H, d, J=6.5 Hz), 0.87 (3H, s), 0.88 (3H, d, J=6.5 Hz), 1.98 (3H, s), 2.14 (1H, br. s, OH), 3.66 (1H, br. s), and 4.86 (1H, br. t, J=9.0 Hz) ppm (Found: C, 72.31; H, 10.95%. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71%).

7 as colorless needles: mp 126—126.5 °C (from hexane); ν_{max} (KBr) 3220 br., 1735, and 1250 cm^{-1}; δ 0.82 (3H, d, J=7.0 Hz), 0.89 (3H, d, J=7.0 Hz), 0.90 (3H, s), 0.98 (3H, d, J=6.5 Hz), 2.01 (3H, s), 3.03 (1H, dt, J=5.2 and 10.0 Hz), and 4.92 (1H, t, J=9.5 Hz) ppm (Found: C, 72.09; H, 11.06%. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71%).

Reaction of the β-Hydroxy Acetate (7) with Mesyl Chloride–Pyridine. Into a solution of **7** (150 mg) in pyridine (1 ml) we stirred mesyl chloride (67 mg), and then the solution was further stirred at room temperature for 3 h and diluted with ether (30 ml). The ethereal solution was washed successively with 10% aq. HCl, water, and a sat. NaCl aq. solution, and then dried over anhydrous Na_2SO_4. The removal of the solvent under reduced pressure afforded colorless prisms of **8** (182 mg); mp 97—100 °C (from hexane); δ 0.82 (3H, d, J=7.0 Hz), 0.89 (3H, d, J=7.0 Hz), 0.92 (3H, s), 0.98 (3H, d, J=6.5 Hz), 1.99 (3H, s), 2.98 (3H, s), 4.16 (1H, dt, J=6.0 and 10.0 Hz), and 4.88 (1H, br. t, J=9.0 Hz) ppm (Found: C, 59.91; H, 9.30%. Calcd for $C_{18}H_{32}O_5S$: C, 59.97; H, 8.95%).

Reaction of the α-Hydroxy Acetate (6) with Mesyl Chloride–Pyridine. Using the same procedure as that used for **7**, the **6** acetate (170 mg) was treated with mesyl chloride (76 mg)-pyridine (2 ml) (room temp, 3 h) to afford colorless prisms of **11** (200 mg); mp 102—103 °C (from hexane–ether); ν_{max} (KBr) 1730, 1250, and 1185 cm^{-1}; δ 0.82 (3H, d, J=7.5 Hz), 0.89 (3H, d, J=7.5 Hz), 0.90 (3H, s), 1.01 (3H, d, J=6.0 Hz), 2.00 (3H, s), 3.02 (3H, s), 4.20 (1H, br. q, J=2.0 Hz), and 4.89 (1H, br. t, J=9.5 Hz) ppm (Found: C, 59.73; H, 9.13%. Calcd for $C_{18}H_{32}O_5S$: C, 59.97; H, 8.95%).

Formation of Two Olefins, 9 and 10. Into a solution of the **8** mesylate (400 mg) in HMPA (5 ml) we stirred NaI (330 mg) under a nitrogen atmosphere. The reaction mixture was further stirred at 80 °C for 3 h and then diluted with AcOEt. The solution was washed with water, and then dried over anhydrous Na_2SO_4. The removal of the solvent under reduced pressure afforded a reddish oil (290 mg), which was separated by preparative TLC [10% $AgNO_3$–SiO_2; hexane–benzene (3:2)] to give **9** (185 mg) and **10** (63 mg).

9 as a colorless viscous liquid: ν_{max} (film) 1740, 1640, and 1250 cm^{-1}; δ 0.82 (3H, s), 0.85 (3H, d, J=5.5 Hz), 0.92 (3H, d, J=5.5 Hz), 1.65 (3H, br. s), 2.04 (3H, s), 4.95 (1H, br. t, J=9.5 Hz), and 5.32 (1H, br. s) ppm; *m/e* 204 (M^+—AcOH), 198 and 161. No elemental analysis of this oil has been carried out, but its structure must be supported by the above-mentioned spectral data, coupled with those of the next experiment, as will be described below.

10 as colorless needles: mp 35—36 °C (by sublimation); ν_{max} (KBr) 1730, 1660, and 1255 cm^{-1}; δ 0.81 (3H, d, J=7.0 Hz), 0.90 (3H, d, J=7.0 Hz), 0.91 (3H, s), 1.01 (3H, d, J=6.5 Hz), 2.06 (3H, s), 5.01 (1H, br. t, J=10.0 Hz), and 5.45 (2H, complex) ppm (Found: C, 76.67; H, 10.93%. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67%).

Reaction of 11 with NaI in HMPA. Using the same procedure as that used for **8**, a solution of **11** (180 mg) and NaI (150 mg) in HMPA (3 ml) was heated at 80 °C for 3 h with stirring, and then treated as usual to give **9** (71 mg) and **10** (27 mg).

Epoxidation of the Trisubstituted Olefin (9). To a solution of **9** (70 mg) in CH_2Cl_2 (5 ml) we added *m*-chloroperbenzoic acid (50 mg). The resulting solution was refluxed for 3 h, then washed successively with 10% aq. Na_2SO_3, 10% aq. $NaHCO_3$, and sat. NaCl aq. solutions, and then dried over anhydrous Na_2SO_4. The removal of the solvent under reduced pressure gave white crystals (70 mg), the sublimation of which afforded colorless prisms of **13**; mp 81—82 °C; ν_{max} (KBr) 1735 and 1250 cm^{-1}; δ 0.84 (3H, s), 0.85 (3H, d, J=5.0 Hz), 0.92 (3H, d, J=5.0 Hz), 1.22 (3H, s), 2.08 (3H, s), 2.87 (1H, br. t, J=2.0 Hz) and 4.92 (1H, dd, J=11.0 and 9.0 Hz) ppm (Found: C, 72.57; H, 10.18%. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06%).

Reduction of the Epoxide (13) with $LiAlH_4$. A mixture of **13** (140 mg) and $LiAlH_4$ (10 mg) in ether (10 ml) was refluxed for 2 h with stirring. After decomposition with ether saturated with water, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give colorless needles of **12**; mp 142.5—143 °C; ν_{max} (KBr) 3200 br. cm^{-1}; δ 0.86 (3H, s), 0.87 (3H, d, J=7.0 Hz), 0.94 (3H, d, J=7.0 Hz), 1.34 (3H, s), 3.61 (1H, br. t, J=8.5 Hz), and 4.19 (2H, br. s, OH) ppm (Found: C, 74.96; H, 12.06%. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74%).

Acetylation of the Diol (12). A solution of **12** (94 mg) in Ac_2O (0.5 ml) and pyridine (1 ml) was stirred at 100 °C overnight, and then diluted with water (10 ml) and extracted with ether. The ethereal extract was washed successively with 10% aq. HCl, 10% aq. NaOH, water, and a sat. NaCl aq. solution, and then dried over anhydrous Na_2SO_4. The removal of the solvent under reduced pressure gave white crystals (102 mg), which were recrystallized from hexane to give colorless needles of **14**; mp 85—86 °C; ν_{max} (KBr) 3330 br., 1735, and 1250 cm^{-1}; δ 0.85 (3H, d, J=7.0 Hz), 0.90 (3H, d, J=7.0 Hz), 0.91 (3H, s), 1.19 (3H, s), 2.06 (3H, s), 2.91 (1H, br. s, OH), and 5.19 (1H, br. t, J=10.0 Hz) ppm (Found: C, 71.95; H, 10.63%. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71%).

Dehydration of the Monoacetate (14). Into a solution of **14** (85 mg) in pyridine (2 ml), we stirred $POCl_3$ (0.5 ml) at 0 °C. The resulting solution was further stirred at 0 °C for 1 h, and at room temperature overnight, and then slowly poured into ice–water and extracted with ether. The ethereal extract was washed successively with 10% aq. HCl and water, and then dried over anhydrous Na_2SO_4. The removal of the solvent under reduced pressure afforded a crystalline solid, which was subsequently purified by preparative TLC using benzene to give white crystals of **15** (75 mg); mp 37—40 °C

(by sublimation); ν_{max} (KBr) 1730, 1655, and 1255 cm^{-1}; δ 0.76 (3H, s), 0.87 (3H, d, J=7.0 Hz), 0.92 (3H, d, J=7.0 Hz), 2.02 (3H, s), 4.45 (1H, br. s), 4.73 (1H, br. s), and 5.00 (1H, br. t, J=9.5 Hz) ppm (Found: C, 76.73; H, 10.88%. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67%).

Formation of (+)-Junenol (1). A mixture of **15** (125 mg) and $LiAlH_4$ (10 mg) in absolute ether (10 ml) was refluxed for 2 h with stirring. After the decomposition of the excess amounts of the reagent with ether saturated with water, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give white crystals (104 mg), the sublimation of which afforded colorless needles of (+)-junenol (mp, optical rotation, and IR spectrum)[1]; δ 0.73 (3H, s), 0.87 (3H, d, J=7.5 Hz), 0.94 (3H, d, J=7.5 Hz), 1.95 (1H, s, OH), 3.63 (1H, br. t, J=10.0 Hz), 4.63 (1H, br. s), and 4.93 (1H, br. s) ppm (Found: C, 80.72; H, 12.03%. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79%).

Oxidation of (+)-Junenol (1). Into a suspension of pyridinium chlorochromate (680 mg) in CH_2Cl_2 (7 ml) we stirred a solution of **1** (70 mg) in CH_2Cl_2 (3 ml) at room temperature. The reaction mixture was further stirred at room temperature for 30 h, and then diluted with absolute ether and filtered. The filtrate was concentrated under reduced pressure to give a brown liquid, which was subsequently separated by preparative TLC using hexane–benzene (1:2) to afford a colorless liquid of acolamone (31 mg) (TLC and IR spectrum) and white crystals of the starting material (30 mg) (mp and IR spectrum).

Reduction of the Acetoxy Olefin (9) with $LiAlH_4$. Into a solution of **9** (112 mg) in absolute ether (10 ml) we stirred $LiAlH_4$ (10 mg), and then the reaction mixture was refluxed for 2 h. After the decomposition of the excess amounts of the reagent with ether saturated with water, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give white crystals (93 mg), the sublimation of which afforded colorless prisms of isojunenol (**2**); mp 77—78.5 °C; ν_{max} (KBr) 3380 br. cm^{-1}; δ 0.78 (3H, s), 0.87 (3H, d, J=7.0 Hz), 0.96 (3H, d, J=7.0 Hz), 1.91 (3H, br. s), 3.51 (1H, br. t, J=10.0 Hz), and 5.36 (1H, br. s) ppm (Found: C, 80.50; H, 12.11%. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79%).

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